CALIFORNIA'S STEM CELL AGENCY

TO: **Members, Governing Board, CIRM**

FROM: **Gil Sambrano, Vice President, Portfolio Development and Review**

DATE: **February 16, 2017**

RE: **Proposed Amendments to CLIN, TRAN, and DISC Concept Plans**

Background

The Board approved a concept plan for CIRM's Clinical ("CLIN") program on December 8, 2014, and additional amendments on July 23 and December 17, 2015. The Board approved concept plans for CIRM's Discovery ("DISC") and Translation ("TRAN") programs on July 23, 2015, and additional amendments on September 24, 2015, and December 13, 2016. The CIRM team has reconsidered these concept plans based on our experience implementing these programs and in light of CIRM's goals. Based on this review, the CIRM team proposes several amendments to the concept plans to further CIRM's goal of accelerating stem cell treatments to patients with unmet medical needs.

The Science Subcommittee met to consider these amendments on January 25, 2017, and recommended them for approval, with questions regarding the proposal to: (1) reduce the timeline to IND filing from 24 months to 18 months for CLIN 1 applicants (readiness eligibility requirement) and (2) replace the minimum percent effort (30%) requirement for principal investigators on CLIN 1 and CLIN 2 awards with a requirement that investigators propose a percent effort consistent with achieving the aims of the project. These two issues are addressed below.

In addition, following the Science Subcommittee meeting, the CIRM team identified several additional proposed clarifications, which are also discussed below, including: (1) explicitly state CIRM's authority to make an eligibility determination until award execution; (2) authorizing CLIN 1 and CLIN 2 (Phase 1) funding for research involving small molecules or biologics that are intended to modify a stem cell therapy, such as a cell tracking agent; (3) reducing the percent effort required for a project manager on TRAN 1, 2, and 3 awards from 50% to 35%; (4) allowing an applicant that has been informed by the FDA that its phase 2 trial could be used as the basis for marketing approval the option to apply as an applicant for phase 3 trial funding; (5) expanding eligibility for a CLIN 3 award to include an existing awardee that is required to conduct new activities, not funded under the parent award, to obtain marketing

approval; and (6) clarifying that allowable project costs for a non-California organization that conducts clinical trials in California include the per subject share of the costs of treating California subjects, including costs incurred out- of-state.

The proposed substantive amendments, including the changes made since the Science Subcommittee meeting, are described below.

Proposed Amendments to CLIN, TRAN, and DISC Concept Plans

1. CIRM Eligibility Determination

Currently, the CIRM team reviews eligibility at the time of the submission of an application. (Eligibility criteria include project readiness, therapeutic type, project manager requirement, co-funding, solvency, good standing, and accuracy/completeness.) If CIRM determines, in its sole discretion, that an application does not meet the eligibility requirements of the program, CIRM will notify the applicant of its decision, and if CIRM deems it appropriate, allow an opportunity to remedy, and if not timely remedied, terminate all further action on the application. In the event CIRM determines that an application does not meet a subjective eligibility criterion for CIRM's clinical program (e.g., whether a therapeutic is being developed for a rare or unmet need unlikely to receive funding from other sources), designated with an asterisk in the program announcement, the applicant may request that the CIRM Grants Working Group (GWG) review the decision. If the GWG affirms CIRM's decision, the applicant will be notified, and no further action will be taken on the application. If the GWG determines the application meets the eligibility requirements, the application will be accepted into the next available clinical review cycle.

On occasion, the CIRM team discovers information later in the process indicating that an applicant was not, in fact, eligible. This often arises as a result of a misunderstanding between the applicant and CIRM that is not discovered until CIRM and the applicant begin to discuss milestones. For example, an investigator may plan to use a cell line for candidate discovery that does not include appropriate consent for commercial use. To date, CIRM has used its authority to establish milestones in order to address eligibility deficiencies that arise after Application Review Subcommittee approval of an award. At times, however, this authority is not sufficient to address the applicant's failure to meet the eligibility requirements. Under these circumstances, CIRM would like to have to authority to terminate work on an award up until the time a contract is executed for failure to meet one or more eligibility criteria, with the exception of those clinical program criteria designated as subjective. CIRM therefore proposes to explicitly state its authority to make an eligibility determination, except with respect to the subjective clinical criteria, until contract execution. This policy change would apply prospectively to awards approved by the Application Review Subcommittee from February 23rd forward, and CIRM will inform the Application Review

Subcommittee at the first available time if it exercises this authority with respect to any award approved by the Subcommittee.

2. Good Standing Eligibility Requirement (CLIN, TRAN, and DISC)

CIRM has long requested that for-profit applicants submit information regarding their financial systems and, since 2014, CIRM has required the officers of for-profits to submit to background checks to determine whether an officer of the organization has been subject to criminal penalties for fraud or misappropriation of funds. Although CIRM, to date, has never had a need to disqualify an applicant based on this information, the eligibility requirements for CIRM's research programs do not currently empower CIRM to disqualify an applicant if CIRM determines that the applicant does not have adequate financial safeguards or if a background check reveals that an officer of the applicant organization has a criminal record involving fraud or misappropriation of funds. Similarly, CIRM has no mechanism to disqualify a proposed principal investigator who is currently under investigation for research misconduct or who has been debarred from receiving federal research funds.

The proposed amendments to the concept plans would add a "good standing" eligibility requirement to address these gaps. This would enable CIRM to disqualify an applicant if CIRM determined that: (1) for for-profits, and non-profits in existence for less than five years, the applicant did not have adequate financial systems in place to track CIRM funds, or the applicant's chief executive officer, chief financial officer, or principal investigator had been convicted of, or was currently under investigation for, crimes involving fraud or misappropriation of funds; and (2) for all applicants, the principal investigator was currently under investigation for research misconduct or was barred from receiving research funds by the Health and Human Services Office of Research Integrity. These changes would allow CIRM to avoid the costs associated with processing an application submitted by an applicant that is not in good standing.

3. Eligibility for Small Molecule or Biologic where Stem Cell is Necessary to Manufacture the Therapy (CLIN 1 and TRAN 1) or that Modifies the Stem Cell Therapy (CLIN and TRAN 1)

Under the current CLIN and TRAN concept plans, CIRM supports preclinical and clinical studies involving small molecules or biologics that act on or are dependent on endogenous stem cells for their therapeutic effect or that are dependent on targeting cancer stem cells for their therapeutic effect and that are being developed for a rare or unmet need unlikely to receive funding from other sources. CIRM proposes to clarify that research involving small molecules or biologics for which a stem cell is necessary to manufacture the therapy is also eligible for funding under CIRM's CLIN 1 and TRAN 1 programs.

In addition, the current CLIN and TRAN 1 concept plans do not authorize funding awards for research involving small molecules or biologics that are intended to modify a stem cell therapy, such as a cell tracking agent. We therefore propose to amend the CLIN and TRAN 1 concept plans to clarify that such research is eligible.

4. Program Manager Eligibility Requirement (CLIN and TRAN 1-3) and Principal Investigator Percent Effort (CLIN)

Under the CLIN concept plan and the concept plan for TRAN 1 and 2, applicants are required to include a project manager on the applicant team to help ensure that the project stays on track and meets its milestones. With the Board's approval of the Translating and Accelerating Center awards, CIRM now has a Stem Cell Center that provides translational and clinical research services to CIRM awardees, including project management services. Rather than requiring applicants to designate an employee or hire an independent contractor, CIRM proposes to allow applicants to satisfy this requirement by entering into a contract with CIRM's Stem Cell Center to provide project management services.

In addition, the TRAN concept plan currently requires that the project manager devote a minimum of 50% effort to the project. Based on discussions with consultants who provide project management services, however, it appears that a project manager can successfully manage a translational project in less time than is currently required. CIRM therefore proposes to reduce the minimum percent effort requirement for a project manager from 50% to 35%.

The CLIN concept plan currently requires principal investigators to commit to a minimum effort of 30%. In some cases, however, the percent effort required by the principal investigator, especially for a clinical trial, may be less and it may vary over time. For example, a principal investigator typically has to devote more time to the trial during the enrollment and treatment phase than during the follow-up phase. Rather than being prescriptive, CIRM proposes to modify the concept plan to require the principal effort to propose and justify a percent effort consistent with achieving the project's aims. However, in light of the questions raised during the Science Subcommittee, we also propose that the percent effort must not be less than an average of 15% over the project period.[1]

5. Readiness Eligibility Requirement (CLIN 1)

Currently, the concept plan for CLIN 1 requires that applicants be prepared to file an IND within 24 months of commencing work on the project. CIRM's strategic plan

[1] We chose 15% based on a survey of clinicians who serve on the Grants Working Group, who advised that 30% was higher than the norm, based on their experience. These members recommended that an appropriate minimum would be between 10% and 20%.

goal, however, is to accelerate the time it takes a stem cell treatment to move from discovery into a clinical trial by 50%. In order to accomplish this goal, we must ensure that CLIN 1 awardees are prepared to file an IND/IDE with the Food and Drug Administration within 18 months of starting work on the project. CIRM therefore proposes to reduce the readiness eligibility requirement for CLIN 1 applicants from 24 months to 18 months.

Members of the Science Subcommittee requested that we provide data regarding the time proposed by applicants to accomplish the activities contemplated by CLIN 1. The average time proposed by the 21 applicants for a CLIN 1 award was 16.8 months, less than the 18 month time period we propose. It therefore appears reasonable at this time to align the concept plan to our strategic plan and propose a goal of 18 months to complete the objective of a CLIN 1 award – the filing of an IND/IDE with the Food and Drug Administration.

6. <u>Clinical Trial Eligibility (CLIN 2)</u>

Under the current CLIN concept plan, small molecules and biologics that act or are dependent on endogenous stem cells or that target cancer stem cells are eligible for funding for all phases of a clinical trial. Because there is a well-known regulatory pathway for the approval of small molecules and biologics, a small molecule or biologic that has promising data after completing a phase 1 trial should be able to obtain funding from other sources to pursue further development. Cellular therapies, by contrast, face a far more challenging regulatory environment and may not be able to obtain sufficient funding for additional development even after obtaining positive data from a phase 1 trial. CIRM therefore proposes to restrict eligibility for phase 2 trials to cellular therapies where stem or progenitor cells either comprise the therapy or are used to manufacture the cell therapy.[2] In addition, because a cellular therapy that has obtained positive data in a phase 2 trial should, in most cases, be able to attract additional funding, CIRM proposes to restrict eligibility for a phase 3 trial to cellular therapies where stem or progenitor cells either comprise the therapy or are used to manufacture the cell therapy and where the therapy is for pediatric or rare indications (e.g., FDA orphan drug designation). For phase 1 trials, CLIN 2 would continue to be open to a small molecule or biologic (**i**) that acts on or is dependent on endogenous stem cells for its therapeutic effect or that is dependent on targeting cancer stem cells for its therapeutic effect. CIRM proposes to clarify that a phase 1 clinical trial involving small molecules or biologics for which a stem cell is necessary to manufacture the therapy or that modify a stem cell therapy is also eligible for funding.

[2] In some cases, the FDA informs a trial sponsor that a phase 2 trial could be used as the basis for marketing approval. Under these circumstances, CIRM proposes to allow the applicant to elect to apply as a phase 3 applicant for purposes of the award caps and co-funding requirement.

7. Award Caps (CLIN)

Under the current CLIN concept plan, awardees may not request more than $20 million for a CLIN 2 (clinical trial) award. To ensure that CIRM funds are spent wisely, CIRM carefully reviews the budget for each CLIN application and rejects budgets that are excessive. Based on CIRM's experience with the CLIN program and the need to ensure that CIRM has sufficient funds available to meet its goals, CIRM proposes to impose caps on all CLIN awards as follows[3]:

CLIN 1 (Late-stage Preclinical):	$6 million (non-profits) $4 million (for-profits)
CLIN 2 (Clinical):	(1) Phase 1 trial: $5 million (for profits) and $9 million (non-profits)
	(2) Phase 2 trial: $12 million
	(3) Phase 3 trial: $15 million
CLIN 3 (Accelerating):	$15 million

8. Eligibility for CLIN 3

Under the current CLIN concept plan, CLIN 3 awards are available to existing clinical awardees who propose to undertake additional activities to accelerate the progress of their clinical project, such as manufacturing improvements and optimization. To date, CIRM has received three CLIN 3 applications but has not yet funded one. Based on the applications submitted to date, CIRM has concluded that this program is not well-designed to achieve CIRM's aims. CIRM therefore proposes to modify the CLIN 3 concept plan to offer an opportunity to existing awardees for an award to support new activities on the awardee's active project that would, if successful, enable the awardee to attain marketing approval of the proposed stem cell treatment with the Food and Drug Administration (FDA). This will serve the goal of accelerating stem cell treatments to patients with unmet medical needs.

[3] These caps are also informed by CIRM's modeling of the numbers and type of awards required to meet CIRM's Strategic Plan goals. See Appendix A for more information.

9. Fundable Activities (CLIN 1 and 2)

Under the current CLIN concept plan, an applicant is barred from engaging in manufacturing activities beyond the manufacture of the candidate therapeutic sufficient to fund a phase 1 trial in the case of CLIN 1, or the proposed trial in the case of CLIN 2. There may be circumstances, however, in which it would be advantageous to manufacture more of the product than is necessary for the immediate trial. Rather than imposing an absolute bar on such manufacturing, CIRM proposes to permit an applicant to propose manufacturing activities for a follow-on clinical trial.

For CLIN 2, CIRM proposes to expand fundable activities to include comparability studies and commercial development activities. Currently, comparability studies are not authorized, but on occasion, the Food and Drug Administration will require comparability studies as part of the regulatory approval process. Similarly, in the case of a registration trial, for example, the Food and Drug Administration requires final formulation packaging and other development activities. Because CIRM's goal is to accelerate stem cell treatments to patients with unmet medical needs, it makes sense to permit applicants to propose such activities in their applications.

In addition, we have clarified that allowable project costs for a non-California organization that conducts clinical trials in California include the per subject share of the costs of treating California subjects, including costs incurred out- of-state.

Of course, the proposed activities, including the budget for manufacturing, would be subject to CIRM review and consideration by the Grants Working Group and the Application Review Subcommittee.

10. Eligibility for Devices (TRAN 3 and CLIN 2)

Under the current TRAN 3 concept plan, CIRM supports studies on a candidate device intended for use in the cure, mitigation, treatment or prevention of disease: (1) where the device is being developed for an intended use with human stem, progenitor or directly reprogrammed cells; (2) where the device is being developed for an intended use that addresses a critical bottleneck to translation, clinical development or use of human stem cell therapies; and (3) where testing with human stem, progenitor or directly reprogrammed cells confirms the utility of the device for stem cell based therapy development. In order to align the TRAN3 program with the CLIN program, CIRM proposes to expand the eligibility requirement for TRAN 3 to include studies on a device where the therapeutic mechanism of action requires the recruitment or incorporation of an endogenous human stem or progenitor cell.

In addition, the current CLIN concept plan imposes no limits on CIRM's funding of device trials. In light of CIRM's limited funding and the well-defined regulatory pathway for devices, CIRM proposes to limit device trials to feasibility. Therefore, CIRM funds would not be available for a pivotal trial for a device.

Requested Action: CIRM requests the Board approve the proposed amendments to the CLIN, TRAN, and DISC concept plans.

Attachments

Appendix

CY2017 - 2020

~$478M in CLIN funding available
40 additional CLIN2 trials to meet our Strategic Plan Goal

CLIN	NP or FP	Est # of Awards	*Award Cap*	CLIN Funding Amount	% Share
CLIN1 - IND	Non-Profit	8	$ *6.0*	$ 48.0	15%
CLIN1 - IND	For-Profit	6	$ *4.0*	$ 24.0	
CLIN2 - Phase 1	Non-Profit	14	$ *9.0*	$ 126.0	33%
CLIN2 - Phase 1	For-Profit	6	$ *5.0*	$ 30.0	
CLIN2 - Phase 2	NP/FP	16	$ *12.0*	$ 192.0	40%
CLIN2 - Phase 3	NP/FP	2	$ *15.0*	$ 30.0	6%
CLIN3 - Phase 2 or 3	NP/FP	2	$ *15.0*	$ 30.0	6%
				$ 480.0	

2.0 CLIN Awards To Date

Program Name	Phase	Grant Number	PI Name	Short Name	Org Status	ICOC Approved Amount	Average	Median	Min	Max
Late Stage Preclinical Projects	IND	CLIN1-08235	Wang, Shaomei	Cedars-Sinai	Non-Profit	$ 4,954,514				
Late Stage Preclinical Projects	IND	CLIN1-08309	Schultz, Peter	CALIBR	Non-Profit	$ 1,667,832				
Late Stage Preclinical Projects	IND	CLIN1-08363	Puck, Jennifer	UCSF	Non-Profit	$ 4,268,865	**$ 4,081,722**	**$ 4,268,865**	**$ 1,667,832**	**$ 5,273,189**
Late Stage Preclinical Projects	IND	CLIN1-08686	Deng, Sophie	UCLA	Non-Profit	$ 4,244,211				
Late Stage Preclinical Projects	IND	CLIN1-09230	Cherqui, Stephanie	UCSD	Non-Profit	$ 5,273,189				
Late Stage Preclinical Projects	IND	CLIN1-08342	Davis, Claude	Angiocrine Bioscience	For-Profit	$ 3,797,117	**$ 3,890,641**	**$ 3,890,641**	**$ 3,797,117**	**$ 3,984,164**
Late Stage Preclinical Projects	IND	CLIN1-08671	D'Amour, Kevin	ViaCyte	For-Profit	$ 3,984,164				
Clinical Trial Stage Projects	Ph1	CLIN2-08289	Abedi, Mehrdad	UC Davis	Non-Profit	$ 8,521,441				
Clinical Trial Stage Projects	Ph1	CLIN2-09444	Lewis, Michael	Cedars-Sinai	Non-Profit	$ 7,354,772	**$ 7,509,826**	**$ 7,354,772**	**$ 6,653,266**	**$ 8,521,441**
Clinical Trial Stage Projects	Ph1	CLIN2-09439	Strober, Samuel	Stanford	Non-Profit	$ 6,653,266				
Clinical Trial Stage Projects	Ph2	CLIN2-08231	Kohn, Donald	UCLA	Non-Profit	$ 7,402,549				
Clinical Trial Stage Projects	Ph2	CLIN2-09339	Kohn, Donald	UCLA	Non-Profit	$ 20,000,000				
Clinical Trial Stage Projects	Ph2	CLIN2-08334	Ascheim, Deborah	Capricor	For-Profit	$ 3,376,259	**$ 9,861,721**	**$ 8,295,750**	**$ 3,376,259**	**$ 20,000,000**
Clinical Trial Stage Projects	Ph2	CLIN2-09577	Chao, Mark	Forty Seven Inc.	For-Profit	$ 10,234,048				
Clinical Trial Stage Projects	Ph2	CLIN2-09698	Klassen, Henry	jCyte, Inc	For-Profit	$ 8,295,750				
Clinical Trial Stage Projects	Ph3	CLIN2-08280	Gringeri, Anthony	ImmunoCellular Therapeutics	For-Profit	$ 19,919,449				
Clinical Trial Stage Projects	Ph3	CLIN2-08938	Lawson, Jeffrey	Humacyte	For-Profit	$ 9,999,528	**$ 15,881,570**	**$ 17,725,734**	**$ 9,999,528**	**$ 19,919,449**
Clinical Trial Stage Projects	Ph3	CLIN2-08239	Dillman, Robert	Caladrius Biosciences	For-Profit	$ 17,725,734				